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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/970,287	10/03/2001	Maria Alexandra Glucksmann	10147-61U1 (MPI2000-471PI	9083

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Intellectual Property Group
MILLENNIUM PHARMACEUTICALS, INC.
75 Sidney Street
Cambridge, MA 02139

EXAMINER	
LACOURCIERE, KAREN A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 11/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant( )	
	09/970,287	GLUCKSMANN ET AL.	
	Examiner	Art Unit	
	Karen A. Lacourciere	1635	

-- The MAILING DATE of this communication appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 August 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *1-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 October 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group IX in the paper filed August 25, 203 is acknowledged. The traversal is on the ground(s) that a search of each of the specific sequence claimed, SEQ ID NO:1, 2 or 3, would not present an undue burden on the Examiner and, therefore, Groups I and II should be rejoined and Groups VII-IX should be rejoined. Applicant has not provided any arguments to traverse the restriction between Groups I-II and Groups VII-IX and each other or any arguments to traverse the restriction of Groups III, IV, V and VI from each other or Groups I, II, VII, VIII and IX. This is not found persuasive because Although there is some overlap in search between each of the Groups, the search is not coextensive, for example, SEQ ID NO:1 includes sequence which is not part of SEQ ID NO:3 and further, the nucleic acids encoding a polypeptide of SEQ ID NO:1 and 3, as claimed, would include polypeptides other than SEQ ID NO:2. For example, the polypeptides encoded by SEQ ID NO:1 or 3, as claimed, need only a portion 60% identity with SEQ ID NO:1 and 3 and are not required to be in frame with the polypeptide encoded by SEQ ID NO:1 or 3 and may include polypeptides with no sequence identity whatsoever with SEQ ID NO:2. Given the extremely broad scope of the claimed invention, the search burden to examine the multitude of polypeptides used in the methods encompassed in the claims.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-27 and SEQ ID NO:1 and 3 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the paper filed 08-25-2003.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Objections

Claim 30 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 30 broadens the subject matter of claim 28 to include methods using any polypeptide that exhibits an epitope in common with a polypeptide having the amino acid sequence of SEQ ID NO:2 and, therefore, does not further limit the subject matter of claim 28.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 28-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In section (ii) of claim 28, the claim recites a fragment of a polypeptide wherein the polypeptide can have alternate embodiments, as the claim recites having "either" an amino acid sequence comprising SEQ ID NO:2, but it is unclear what those alternatives are because the only other alternative listed in section (ii) of the claim is not a polypeptide, but rather a cell. Therefore, it is unclear what methods are encompassed by the claims. Claims 29 and 30 are indefinite for the same reasons due to dependence on claim 28.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 28-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The specification discloses SEQ ID NO: 1 and 3 which correspond to the cDNA/genomic DNA encoding the human species of 22437 protein, SEQ ID NO:2. SEQ ID NO: 2, and fragments of SEQ ID NO:2, meet the written description provisions of 35 USC 112, first paragraph. However, claims 28-30 are directed to encompass methods using polypeptides and fragments of polypeptides encompassing a much broader scope than described by SEQ ID NO:2, or polypeptides encoded by SEQ ID NO:1 and 3, for examples, the claims encompass polypeptide fragments comprising 15 amino acid residues from SEQ ID NO:2, but further comprising an unlimited number of amino acid residues not described by SEQ ID NO:2 or described by the sequences encoding polypeptides, SEQ ID NO:1 or 3. This would, for example, encompass 22437 polypeptides from species other than human, that may comprise one common region with the human version, mutated sequences of human 22437 polypeptide, allelic variants, splice variants, polypeptides and fragments of polypeptide encoded by sequences that have a portion of a sequence with 60% degree of identity with SEQ ID NO:1 or 3, and so forth. The claims are so broad as to encompass fragments of a polypeptide which have no identity with the one described polypeptide, SEQ ID NO:2, since the polypeptide need only be encoded by a nucleic acid with a portion of a sequence 60% identical to SEQ ID NO:1 or 3, and therefore, may not be in frame to encode an amino acid sequence with any identity to SEQ ID NO:2. Further, the portion of the nucleic acid sequence 60% identical to SEQ ID NO:1 or 3 is not required to be within the region of the nucleic acid encoding the polypeptide and, therefore, would

encompass polypeptides not described by the specification at all. Claim 30 extends the scope further, to include polypeptides with a common epitope with SEQ ID NO:2, however, this would encompass polypeptides with little or no amino acid sequence similarity with SEQ ID NO:2, for example, methods using polypeptides comprising epitopes with similar tertiary elements but little or no common amino acids would be encompassed in the claimed methods, or, for example, would encompass fragments of polypeptides with a common epitope, wherein the fragment itself does not encompass the common epitope, none of the broad genus of these polypeptides are described in the specification. None of these sequences meet the written description provision of 35 USC 112, first paragraph. The specification provides insufficient written description to support the very broad genus of polypeptides and fragments of polypeptides used in the methods encompassed by the claims.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of SEQ ID NO: 2 and fragments of SEQ ID NO:2, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides or fragments of polypeptides, regardless of the

complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.* , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli* , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood* , 107 F.3d at 1572, 41 USPQ2d at 1966.
>
> An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. *Fiers v. Revel* , 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

> The name cDNA is not itself a written description of that DNA; it conveys no distinguishing information concerning its identity. While the example provides a process for obtaining human insulin-encoding cDNA, there is no further information in the patent pertaining to that cDNA's relevant structural or physical characteristics; in other words, it thus does not describe human insulin cDNA. Describing a method of preparing a cDNA or even describing the protein that the cDNA encodes, as the example does, does not necessarily describe the cDNA itself. No sequence information indicating which nucleotides constitute human cDNA appears in the patent, as appears for rat cDNA in Example 5 of the patent. Accordingly, the specification does not provide a written description of the invention of claim 5.

Therefore, only methods using polypeptides comprising SEQ ID NO: 2 or fragments of SEQ ID NO:2, but not the full breadth of the claims, meet the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

Claims 28-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)): the breadth of the

claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Claims 28-30 are drawn to methods of identifying a compound useful for modulating at least one phenomena selected from the group consisting of tumor establishment, epithelial cell proliferation, endothelial cell proliferation, neuronal cell growth, wound healing and cerebral injury healing, wherein a 22437 polypeptide (SEQ ID NO:2), a fragment of a 22437 polypeptide (SEQ ID NO:2), or a broad genus of polypeptides related to a 22437 polypeptide (e.g., polypeptides or fragments of a polypeptide with a common epitope to SEQ ID NO:2 or polypeptides encoded by a sequence with a portion of the sequence being at least 60% identical to SEQ ID NO:1 or 3) is contacted with a test compound and binding is assessed.

Claims 28-30 are very broad, encompassing methods wherein binding of generally any type of compound is tested for binding to a broad range of highly variant polypeptides, a major portion of which have not been described, and, therefore, also not characterized by the instant specification. As claimed, these methods are directed to identifying compounds which modulate a very broad range of phenomena, which occur in a broad range of types of cells and tissues. These effects occur in vitro, in cells in culture, and in vivo, in a whole organism, with a broad range of physiological effects. The evaluation of the ability of the test compound to modulate this very broad range of effects in a very broad genus

of cell and tissue types is based purely on the binding of the compound to a polypeptide, without any evaluation of the effect of the compound on the target polypeptide, for example, whether it inhibits or increases the activity of the polypeptide and how that would relate to the modulation of any of the specifically claimed phenomena, the degree of binding, for example, whether the specificity or strength of binding is sufficient to produce any meaningful physiological outcome related to the specifically claimed phenomena, nor has the specification provided the guidance to determine such. Further, the claims are so broad as to encompass methods wherein the binding of a compound to a fragment of a polypeptide is assessed, whether or not the fragment has any relevance physiologically, for example, whether the fragment used in the assay folds to resemble the protein as it would occur in a cell and, therefore, whether the fragment has any possible meaning in relation to the specifically claimed phenomena. As claimed, the methods assess binding may determine compounds that bind to a polypeptide, however, simple binding would not provide any reliable information regarding a compound's ability to modulate any of the physiological effects the claimed methods directed to. Further, the specification has not provided any guidance to enable the skilled artisan to extend the determination of binding to provide any meaningful information to determine if a compound modulates the very broad range of physiological phenomena claimed. Simple determination of binding would not predictably translate into an ability of a compound to modulate any physiological phenomena, as claimed.

Further, the specification discloses one particular preferred embodiment of the polypeptide used in the claimed methods, SEQ ID NO:2, but it is unclear whether SEQ ID NO: 2, or any polypeptide or fragment thereof, related to SEQ ID NO:2 has any effect on the claimed phenomena in a cell. The specification discloses that SEQ ID NO:2 is a predicted polypeptide sequence encoded by nucleic acid sequences which are expressed differentially when cells were grown in soft agar versus plastic (see example 5). The expression of these nucleic acids also appeared to be high in many normal tissue types, diseased tissues and in xenograft cell lines (see table 5 and 6 and results summary page 95). The results of expression profiling of the nucleic acids encoding SEQ ID NO:2, discussed on pages 101-102, indicate there is variability in expression levels among different tumor tissues and normal tissue types. The variable nature of the expression indicates that although nucleic acids encoding SEQ ID NO:2 may be differentially expressed in some tissue types and some cancer tissues, it is unclear how these expression levels correlate with any particular physiological conditions. Further, a differential level of expression of these nucleic acids would not predictably correlate with the modulation of any of the specifically claimed phenomena, as assessed in the claimed methods. For example, it is unclear that the expression levels of these nucleic acids is involved in the regulation of any physiological phenomena, or, for example, a response to a disease condition. For example, if the differential expression is a response to a disease state, binding a compound to the polypeptide product, even if it modulates activity of the polypeptide, would not modulate the physiological phenomena claimed. The

specification has given virtually no guidance on the actual activity of the polypeptide encoded by these nucleic acids (SEQ ID NO:2) except to speculate that the protein is a novel sulfatase, based on sequence similarity with other potential sulfatases, and its relation to the specifically claimed phenomena is based on speculation that other members of the sulfatase family may be involved in these physiological phenomena. The level of guidance provided by the specification about the specifically claimed polypeptide is scant and the skilled artisan would not predictably expect to determine compounds that modulate the broad range of physiological phenomena as claimed.

To practice the claimed methods, the skilled artisan would need to undergo undue trial and error experimentation, beyond the teachings and guidance of the specification, to determine compounds that modulate the broad range of physiological phenomena claimed, for the broad range of tissue and cell types encompassed in the claims. Even through such undue trial and error experimentation, it is unpredictable that the skilled artisan would ever be able to determine such compounds, since it is unclear that SEQ ID NO:2 is even involved in the broad range of specified phenomena or if determination of binding to SEQ ID NO:2 would provide any information on a compounds ability to modulate such phenomena.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Nagase et al. (DNA Research 6, 337-345 (1999) is cited

because it discloses a nucleic acid encoding a polypeptide 100% identical to SEQ ID NO:2 of the instant application (Hypothetical protein KIAA1247, proposed to be a sulphatase), however, it does not disclose the instantly claimed and elected methods of screening using said protein.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Lacourciere whose telephone number is (703) 308-7523. The examiner can normally be reached on Monday-Thursday 7:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

KAREN A. LACOURCIERE, PH.D
PRIMARY EXAMINER

Karen A. Lacourciere
November 13, 2003